

TENT COOPERATION TREATY

PCT

13 Rec'd PCT/PTO 14 JAN 2002
09/509032

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 2059-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE99/02316	International filing date (day/month/year) 10.12.1999	Priority date (day/month/year) 14.12.1998
International Patent Classification (IPC) or national classification and IPC: C 07 D 207/16, C 07 D 405/06, A 61 K 31/10		
Applicant AstraZeneca Aktiebolag et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 30.06.2000	Date of completion of this report 17.04.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Göran Karlsson/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/SE99/02316

1. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description: _____, as originally filed
pages 1-81 _____, filed with the demand
pages _____, filed with the letter of _____
pages _____
- ☒ the claims: _____, as originally filed
pages 82-83, 86-88, 90-93 _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of 04-04-2001
pages 84-85, 89, 94
- ☐ the drawings: _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
pages _____
- ☐ the sequence listing part of the description: _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
pages _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE99/02316

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 21-23

because:

☒ the said international application, or the said claims Nos. 21-23
relate to the following subject matter which does not require an international preliminary examination (*specify*):

A method for treatment of the human and animal body by therapy
(PCT Rule 67.1 (iv))

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE99/02316

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-20, 24</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-20, 24</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-20, 24</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The invention relates to amidino derivatives, their use as medicaments, pharmaceutical compositions containing them and synthetic routes to their production. The invention also relates to the use of these compounds as an active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

WO, A, 9632110 discloses thrombin inhibiting compounds which contain an N-amidinopiperidinylmethyl group (see especially claim 5 page 42 and page 19 table 2).

Claims 1-20 and 24 of 04-04-2001 are considered to be novel. Further, there is no information in WO, A, 9632110 which would lead a person skilled in the art that these compounds are useful as thrombin inhibitors. Thus, claims 1-20 and 24 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

WO, A, 9857932 (publication date 23.12.98) discloses amidino derivatives which are useful as thrombin inhibitors. No specific compound according to this document has been found to be included in the present claims. WO, A, 9857932 is therefore not considered to hinder a patent.

WO, A, 9625426 further discloses the general state of the art which is not considered to be of particular relevance.

*** RX REPORT ***

RECEPTION OK

TX/RX NO	9535	
CONNECTION TEL		703+816+4100
SUBADDRESS		
CONNECTION ID		
ST. TIME	01/14 12:50	
USAGE T	01'35	
PGS.	9	
RESULT	OK	

selected from C_{1-4} alkyl, C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo substituent), methylenedioxy, halo, hydroxy, cyano, nitro, $S(O)_2NH_2$, $C(O)OR^{26}$, SR^{26} , $S(O)R^{26a}$, $S(O)_2R^{26a}$ or $N(R^{27})R^{28}$;

- 5 R^3 represents one or more optional substituents selected from OH, C_{1-4} alkoxy, C_{1-6} alkyl (optionally substituted by one or more halo group), or $N(R^{29a})R^{29b}$;

R^{25} , R^{29a} and R^{29b} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$;

R^{26} represents H or C_{1-4} alkyl;

- 10 R^{26a} represents C_{1-4} alkyl;

R^{27} and R^{28} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$, or together represent C_{3-6} alkylene, thus forming a 4- to 7-membered ring, which ring is optionally substituted, on a carbon atom that is α to the nitrogen atom, with an =O group;

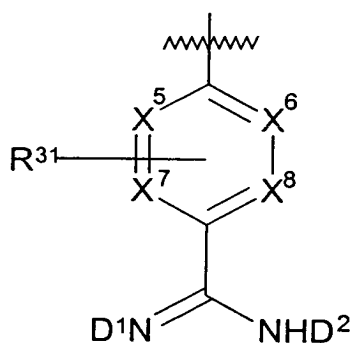
- 15 R^{21} , R^{22} , R^{23} , R^{24} and R^{30} independently represent, at each occurrence, H or C_{1-4} alkyl;

Y represents CH_2 , $(CH_2)_2$, $CH=CH$ (which latter group is optionally substituted by C_{1-4} alkyl), $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$ (which
20 latter three groups are optionally substituted by C_{1-4} alkyl, methylene, =O or hydroxy);

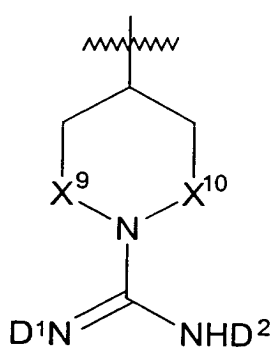
R^y represents H or C_{1-4} alkyl;

- 25 n represents 0, 1, 2, 3 or 4; and

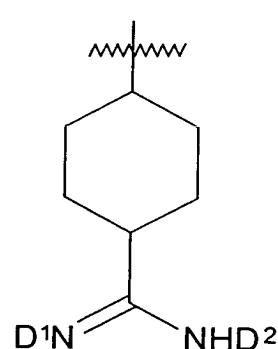
B represents a structural fragment of formula IIIa, IIIb or IIIc



IIIa



IIIb



IIIc

wherein

X^5 , X^6 , X^7 and X^8 independently represent CH, N or N-O;

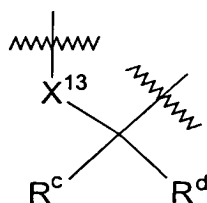
X^9 and X^{10} independently represent a single bond or CH_2 ;

- 5 R^{31} represents an optional substituent selected from halo, C_{1-4} alkyl (which group is optionally substituted by one or more halo group), $N(R^{32})R^{33}$, OR^{34} or SR^{35} ;

R^{32} and R^{33} independently represent H, C_{1-4} alkyl or $C(O)R^{36}$;

R^{34} , R^{35} and R^{36} independently represent H or C_{1-4} alkyl; and

- 10 one of D^1 and D^2 represents H, and the other represents H, OR^a , NHR^a , $C(=X^{11})X^{12}R^b$, or D^1 and D^2 together represent a structural fragment of formula IVa:-



IVa

R^a represents H or $-A^5[X^{14}]_n[C(O)]_rR^c$;

- 15 R^b represents $-A^5[X^{14}]_n[C(O)]_rR^c$;

A^5 represents, at each occurrence, a single bond or C_{1-12} alkylene (which alkylene group is optionally interrupted by one or more O, $S(O)_m$ and/or

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Ch);
 (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-allyl);
 (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Bzl);
 (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
 5 (CO-O-methallyl);
 1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab(OH);
 (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Val);
 (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-(Me)Pab; or
 9-hydroxyfluoren-9-yl-C(O)-Aze-Pab x HOAc.

10

2. A compound as claimed in Claim 1 wherein R¹ represents OH or C₁₋₄ alkyl (which latter group is optionally substituted by cyano or OH).

15

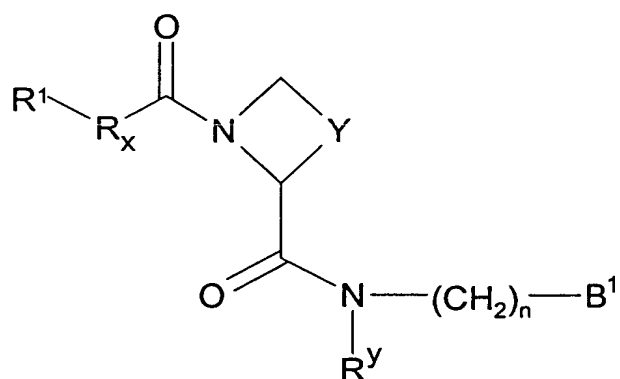
3. A compound as claimed in any one of the preceding claims wherein R_x represents a structural fragment of formula IIa or IIb.

20

4. A compound as claimed in any one of the preceding claims wherein, when R_x represents a structural fragment of formula IIa, then the dotted lines represent bonds, A and E both represent CH and D represents -CH=CH-;

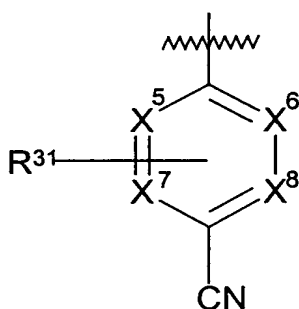
25

5. A compound as claimed in any one of the preceding claims wherein, when R_x represents a structural fragment of formula IIa, X₁ represents optionally unsaturated C₂- or C₃-alkylene, or -Z-A³ (in which Z represents O, S(O)_m or N(R²⁵) (in which R²⁵ is as defined in Claim 1 or represents C₁₋₄ alkyl or C(O)R³⁰ and m and R³⁰ are as defined in Claim 1) and A³ represents C₁- or C₂-alkylene (which latter group is optionally unsaturated)).

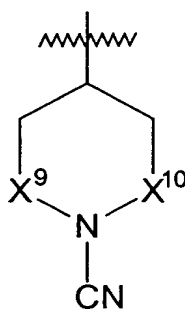


VIII

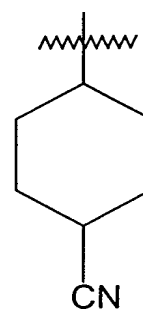
wherein B¹ represents a structural fragment of formula IIIId, IIIe or IIIf



IIIId



IIIe



IIIIf

and R¹, R_x, Y, R^y, n, R³¹, X⁵, X⁶, X⁷, X⁸, X⁹ and X¹⁰ are as defined in
 5 Claim 1 with a compound of formula IX,



IX

wherein X^a represents O or NH and R^a is as defined in Claim 1;

- (iv) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, reaction of a compound of formula I in which D¹ or D² (as
 10 appropriate) represents C(O)OR^{b1}, in which R^{b1} represents a protecting group with a compound of formula IX as defined above;
- (v) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, in which A⁵ does not represent a single bond, and n represent 1, reaction of a compound of formula I in
 15 which D¹ or D² (as appropriate) represents OH or NH₂, with a compound

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA AB
Global Intellectual Property,
Patents
S-151 85 Södertälje
SUÈDEDate of mailing (day/month/year)
30 August 2000 (30.08.00)Applicant's or agent's file reference
H 2059-1 WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE99/02316International filing date (day/month/year)
10 December 1999 (10.12.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

LINSCHOTEN, Marcel
Astra Hässle AB
S-431 83 Mölndal
Sweden

State of Nationality

NL

State of Residence

SE

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

LINSCHOTEN, Marcel
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

State of Nationality

NL

State of Residence

SE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

A. Karkachi

Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREA

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Global Intellectual Property,
Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year) 30 August 2000 (30.08.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference H 2059-1 WO	
International application No. PCT/SE99/02316	International filing date (day/month/year) 10 December 1999 (10.12.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address NYSTRÖM, Jan-Erik Astra Pain Control AB S-151 85 Södertälje Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address NYSTRÖM, Jan-Erik AstraZeneca R&D Södertälje S-151 85 Södertälje Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Global Intellectual Property,
Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year) 30 August 2000 (30.08.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference H 2059-1 WO	
International application No. PCT/SE99/02316	International filing date (day/month/year) 10 December 1999 (10.12.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address KARLSSON, Olle Astra Hässle AB S-431 83 Mölndal Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address KARLSSON, Olle AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38
--	---

PCT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
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Applicant's or agent's file reference H 2059-1 WO	
International application No. PCT/SE99/02316	International filing date (day/month/year) 10 December 1999 (10.12.99)

1. The following indications appeared on record concerning:	
<input checked="" type="checkbox"/> the applicant	<input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address INGHARDT, Tord Astra Hässle AB S-431 83 Mölndal Sweden	State of Nationality SE
	State of Residence SE
	Telephone No.
	Facsimile No.
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:	
<input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence	
Name and Address INGHARDT, Tord AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	State of Nationality SE
	State of Residence SE
	Telephone No.
	Facsimile No.
3. Further observations, if necessary:	
4. A copy of this notification has been sent to:	
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 August 2000 (30.08.00)	
International application No. PCT/SE99/02316	Applicant's or agent's file reference H 2059-1 WO
International filing date (day/month/year) 10 December 1999 (10.12.99)	Priority date (day/month/year) 14 December 1998 (14.12.98)
Applicant INGHARDT, Tord et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
30 June 2000 (30.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Global Intellectual Property,
Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year)

30 August 2000 (30.08.00)

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IMPORTANT NOTIFICATION

International application No.

PCT/SE99/02316

International filing date (day/month/year)

10 December 1999 (10.12.99)

1. The following indications appeared on record concerning:

☐

the applicant

☐

the inventor

☒

the agent

☐

the common representative

Name and Address

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
Sweden

State of Nationality

State of Residence

Telephone No.

46 8 553 260 00

Facsimile No.

46 8 553 288 20

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐

the person

☐

the name

☒

the address

☐

the nationality

☐

the residence

Name and Address

ASTRAZENECA AB
Global Intellectual Property,
Patents
S-151 85 Södertälje
Sweden

State of Nationality

State of Residence

Telephone No.

46 8 553 260 00

Facsimile No.

46 8 553 288 20

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

A. Karkachi

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38